In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the May 30, 2003 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides a small molecular weight tumor necrosis factor receptor molecule and related methods. This receptor molecule binds TNF and comprises all or a functional portion of at least two extracellular domains of TNF receptors linked via one or more polypeptide linkers. The polypeptide linkers are from about 10 to about 30 amino acids in length.

The claimed receptor molecule shows *surprising* advantages over other multi-TNF receptor-based molecules. Specifically, the instant molecule, as exemplified by Hu TNF-R75 ECD, shows the same anti-TNF-specific activity as an Ig-based TNF receptor molecule - and at *only a third of the concentration* required for the Ig-based molecule. Even more dramatic is the fact that a concentration of TNF receptor monomer 300-fold higher than that tested for the instant molecule *was ineffective*.

The claimed molecule is characterized by a low molecular weight, an optimal linker length, and the absence of an Ig Fc domain which has the potential to cause side effects. These features combined make this molecule unexpectedly superior to known TNF receptor-based molecules.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-3, 6, 8, 14-17 and 19-37 under 35 U.S.C. §103(a) as allegedly unpatentable over Wallach, et al. (U.S. Patent No. 5,478,925, "Wallach I") or Wallach, et al. (EP 0 526 905, "Wallach II").

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants incorporate herein by reference their remarks made in their October 15, 2001 Amendment and their August 19, 2002 Communication.

Claims 1-3, 6, 8, 14-17 and 19-37 provide a small molecular weight TNF receptor-based molecule and methods of using same. This molecule binds TNF and comprises all or a functional portion of two extracellular domains of TNF receptors linked via one or more polypeptide linkers of 10-30 amino acids in length.

As stated already, the claimed molecule is characterized by a low molecular weight, an optimal linker length, and the absence of an Ig Fc domain which has the potential to cause side effects. These features combined make this molecule unexpectedly superior to known TNF receptor-based molecules.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First the cited references, when combined, must teach or suggest every element of the claims. Second, one of ordinary skill must have been motivated to combine the teachings of the cited references at

the time of the invention. Third, there must be a reasonable expectation that the claimed invention would succeed.

Here, each of the cited references fails to support a *prima facie* case of obviousness. To support a *prima facie* case of obviousness, each of Wallach I or Wallach II, in view of routine skill in the art, would at a minimum have to teach or suggest every element of the claims.

Neither Wallach I nor Wallach II does this.

Specifically, each reference teaches TNF receptor multimers. These multimers are made from monomers held together by *any* means (see Wallach II, page 2, lines 44-46). For example, the monomers may be held together by both covalent bonding, such as via chemical cross-linkers, as well as non-covalent bonding, such as via liposome formation. As stated in previous responses, joining monomers covalently via a peptide linker is but only one method out of a veritable universe of possibilities taught by the references.

The Examiner incorrectly relies on the teaching of Wallach I and II that "those of ordinary skill in the art will be able to determine" the [linker] length for optimum activity. At most, the *possibility* that one skilled in the art could have optimized a linker length using routine experimentation is merely an invitation to experiment further. Such a possibility, as taught by the art, does not constitute the teaching of the linker length, i.e., 10-30 residues, which applicants actually conceived. Thus, the cited references fail to teach or suggest all elements of the rejected claims.

Moreover, when combined with routine skill, Wallach I and II also fail to provide a reasonable expectation of success. These references offer no experimental evidence demonstrating the success of their claimed multimers. They also fail to give guidance as to how one would arrive at a linker length which would provide the unexpected advantages seen with the instant molecule. Thus, neither reference provides a reasonable expectation of success and, indeed, creates at best an invitation to experiment further.

In light of these references and their shortcomings, the Examiner has failed to show how either cited reference teaches or suggests every element of the claims, or provides a reasonable expectation of success for the claimed invention. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1-3, 6, 8, 14-17 and 19-37 over Wallach I or II, in view of routine skill in the art at the time of the invention.

The Examiner also rejected claims 1-3, 6, 8, 14-17 and 19-37 under 35 U.S.C. §103(a) as allegedly unpatentable over Smith, et al. (U.S. Patent No. 5,395,760).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The rejected claims are discussed above.

Smith, et al. teach that "both monovalent and polyvalent forms of TNF-R are useful in the compositions and methods of the invention...[f]or example, a bivalent soluble TNF-R may consist of two tandem repeats of amino acids 1-235 of FIG. 2A, separated by a linker region" (see column 10, lines 33-39). Smith, et al. do not define the optimal length of this linker region. Instead, Smith, et al. focus on providing examples of polyvalent forms of TNF-R constructed by chemical coupling techniques. In essence, Smith, et al. suffer the same deficiency seen in Wallach I and II, i.e., they teach a receptor-based molecule with a virtually infinite number of linker permutations. In combination with routine skill in the art, Smith, et al. cannot be construed to teach or suggest a receptor-based molecule comprising a *peptide* linker of a *defined* length, i.e., 10-30 residues, as in the claimed invention. Thus, this reference, in combination with routine skill, fails to teach or suggest all elements of the rejected claims, and fails to provide a reasonable expectation of success.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1-3, 6, 8, 14-17 and 19-37 over Smith, et al., in view of routine skill in the art at the time of the invention.

In view of the above remarks, applicants maintain that claims 1-3, 6, 8, 14-17 and 19-37 satisfy the requirements of 35 U.S.C. §103(a).

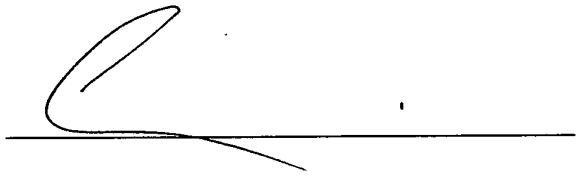
Summary

In view of the foregoing remarks, applicants respectfully request that the above grounds of rejection be reconsidered and withdrawn and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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